REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim 1 has been amended to incorporate the limitations of claim 2. Claim 2 is cancelled. The process according to claim 1 as amended is explained on pages 21-22 of the specification. Claim 3 has been amended for clarification purposes in conformance with U.S. practice. See page 23. Claims 7, 14 and 18 are amended in conformance with U.S. practice. Claim 17 is cancelled. The claims pending after the foregoing amendments are claims 1, 3-16 and 18.

Turning to the Official Action, claims 1-18 are rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over the claims of U.S. Patent No. 6,482,864.

A Terminal Disclaimer is submitted in conformance with U.S. practice.

Accordingly, this ground of rejection is deemed to be overcome.

The cancellation of claim 17 overcomes the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U.S. Patent No. 6,191,107.

Cancellation of claim 17 further overcomes the 102 rejection as based upon WO 97/01331.

Lastly, claims 1-18 are rejected under 35 USC 103 as being unpatentable over WO 97/01331. This ground of rejection is deemed to be overcome as applied to the claims as amended, and further in view of the Rule 132 Declaration of Mr. Yamagata submitted herewith.

The claims have been limited to the feature that the protein-containing solution is applied or dropped on the refrigerant carrier. In contrast, the cited reference teaches spray drying the protein-containing solution.

The Declaration describes Examples 3, 4, 7-9, Experimental Examples 1 and 2, and Figure 1 of the present application.

As seen from the Declaration, the frozen protein powder obtained by application of the protein-containing solution to the refrigerant carrier to quickly freeze the solution maintains a much higher-order structure of the protein in comparison with the frozen protein powder obtained

by spraying the solution to quickly freeze the solution. Further, the amount of the protein transferred into the body from the microcapsules prepared with the protein powder obtained by quick freezing by application is significantly higher than that of the microcapsules prepared with the protein powder obtained by quick freezing by spraying.

These results have not been reported heretofore in the prior art and are unexpected.

On the other hand, the reference relied upon by the Examiner does not teach or suggest the above feature of the amended claims.

Thus, it is believed that the amended claims are patentable over the reference.

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome.

Accordingly, favorable reconsideration and allowance is respectfully solicited.

Respectfully submitted,

Yutaka YAMAGATA et al.

By: Warren M. Cheek, Jr.

Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
October 14, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Yutaka YAMAGATA et al. :

Serial No. 10/088,142 : Group Art Unit 1615

Filed: March 15, 2002 : Examiner: R. M. Bennett

For: PROCESS FOR PRODUCING PROTEIN POWDER

DECLARATION UNDER RULE 1.132

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Yutaka YAMAGATA, a citizen of Japan and residing in Hyogo-ken, Japan declare and say that:

1. I graduated from the Osaka University, Japan, in 1986, and finished the master course of Faculty of Fundamental Engineering at the Osaka University, Japan, in 1988.

2. Since April, 1988 up to this time, I have been an employee of Takeda Chemical Industries, Ltd., the assignee of the above-identified application, and engaged in the research of drug formulation. At present, I am an Assistant Research Head of Drug Formulation Research Laboratories, Pharmaceutical Research Division, Pharmaceutical Group of said company.

3. I am one of the co-inventors of the above-identified application and am familiar with the subject matter thereof.

4. I have read the Office Action mailed June 12, 2003 and the references cited therein and am familiar with the subject

matter thereof.

5. In order to show unexpected results by the process claimed in the above-identified application, Examples 3, 4 and 7 to 9 and Experimental Examples 1 and 2 disclosed in the specification of the above-identified application as well as Fig. 1 attached thereto are set forth below.

Example 3

Freezing of an aqueous hGH solution and subsequent vacuum drying

Twenty-fold molar equivalent of ammonium acetate was added to an aqueous solution of gene recombinant type hGH (the final concentration of hGH = 2 mg/mL) and the mixture was filtered through a 0.22 μm filter to prepare a solution formulation for freeze-drying (Formulation 2). After cooling the solution below 10°C, given amount portions thereof of about 0.3 to 0.5 mm fluid diameter were applied to a tray (area: about 1,300 cm^2) on a freeze-dryer shelf cooled at -45 to -40°C every 5 minutes, and freeze-dried (Triomaster A04: Kyowa Vacuum (condensation capacity 10 kg type)) to prepare a lyophilized powder (hereinafter abbreviated as hGH powder). The temperature of the tray during application was -40 to -30°C. By using the resulting hGH powder, the average particle size of the finely divided hGH powder was measured according to the same manner as that described in Example 1.

Table 3 shows the average particle size of the finely divided hGH powder obtained by freezing Formulation 2 according

to the above process. The mean cooling rate of Formulation 2 became -201.0°C/min. (maximum -203.7°C/min.) to -72.5°C/min. (minimum -54.6°C/min.) by adjusting the amount of application to the tray to 10 mL/5 min. to 86 mL/5 min. Thus, it was possible to control the average particle size of the finely divided hGH powder to 1.4 μm to 4.7 μm.

Table 3

	Application Amount (amount (mL) per 5 min./tray)			
	10	60	70	86
Average particle size (μm)	1.4	2.3	3	4.7
Mean cooling rate (°C/min.)	-201.0	-88.7	-84.1	-72.5

Example 4

Freezing of an aqueous hGH solution and subsequent vacuum drying

Formulation 2 was prepared. The temperature was adjusted to room temperature, and given amount portions thereof of about 0.3 to 0.5 mm fluid diameter were applied to a tray (area: about 1,300 cm^2) on a freeze-dryer shelf cooled at -45 to -40°C every 5 minutes, and freeze-dried (RL-603BS: Kyowa Vacuum (condensation capacity 10 kg type)) to prepare hGH powder aseptically. The temperature of the tray during application was -40 to -30°C. By using the resulting hGH powder, the average particle size of the finely divided hGH powder was measured according to the same manner as that described in Example 1.

Table 4 shows the average particle size of the finely divided hGH powder obtained by freezing Formulation 2 according to the above process. The mean cooling rate of Formulation 2

became -84.6°C/min. (maximum -87.4°C/min.) to -67.3°C/min. (minimum -54.9°C/min.) by adjusting the amount of application to the tray to 50 mL/5 min. to 80 mL/5 min. Thus, it was possible to control the average particle size of the finely divided hGH powder to 2.7 μm to 5.5 μm.

Table 4

	Application Amount (amount (mL) per 5 min./tray)			
	50	60	70	80
Average particle size (μm)	2.7	2.7	3.2	5.5
Mean cooling rate (°C/min.)	-84.6	-80.6	-76.6	-67.3

Example 7

Freezing of an aqueous hGH solution and subsequent vacuum drying

The aqueous hGH solution of Formulation 2 was prepared. The solution was adjusted to room temperature and given amount portions thereof were sprayed intermittently to a tray (area: about 1,300 cm^2) on a freeze-dryer shelf cooled at below -25°C , and freeze-dried (Triomaster A04: Kyowa Vacuum (condensation capacity 10 kg type)) to prepare a hGH powder. By using the hGH powder, the average particle size of the finely divided hGH powder was measured according to the same manner as that described in Example 1.

Table 12 shows the average particle size of the finely divided hGH powder obtained by freezing Formulation 2 according to the above process. When the rate of spraying Formulation 2 to the tray was controlled to 50 mL/5 min. to 100 mL/5 min.,

the mean cooling rate of Formulation 2 became -65.3°C (maximum -73.9°C/min.) to -37.3°C/min. (minimum -34.3°C/min.) and it was possible to control the average particle size of the finely divided hGH powder to 1.5 μm to 9.5 μm by controlling the dropping rate to 60 mL/5 min. to 140 mL/5 min.

Table 12

	Spraying rate (amount (mL) per 5 min./tray)		
	50	80	100
Average particle size (μm)	1.5	2.9	9.5
Mean cooling rate (°C/min.)	-65.3	-43.3	-37.3

Example 8

Production of microcapsules including hGH

To a solution of 1.85 g of a lactic acid/glycolic acid copolymer (lactic acid/glycol acid = 50/50, average molecular weight as converted value to polystyrene = 13,000, viscosity = 0.145 dL/g) and 10 mg of zinc oxide in 2.7 mL of dichloromethane was added 140 mg of the hGH powder obtained in Example 3, the amount of application of 10 or 60 (amount for 5 min. (mL) per tray). Then, it was atomized by using Polytron (commercially available from Kinemachica). The S/O dispersion was added to 800 mL of an aqueous solution of 0.1% polyvinyl alcohol. Then, the resulting liquid was stirred and emulsified using a homomixer. Dichloromethane was evaporated with stirring for 3 hours at room temperature and then the dispersion was centrifuged (about 1,800 rpm) to collect microcapsules. Subsequently, the microcapsules were washed 2 times with 400 mL of distilled water,

followed by addition of 0.2 g of D-mannitol and then freeze-drying. Further, the resulting substance was dried in vacuo at 46°C for 3 days for removing the remaining solvent. Thus, 2 kinds of microcapsules including hGH were obtained.

Example 9

Production of microcapsules including hGH

According to the same manner as that described in Example 8, 2 kinds of microcapsules including hGH were obtained by using the hGH powder prepared in Example 7, the spraying amount of 50 and 80 (amount for 5 min. (mL)/tray).

Experimental Example 1

in vivo Release profile

The microcapsules obtained in Examples 8 and 9 were subcutaneously administered to immuno-suppressed SD rats (male, aged 6 weeks) (6 mg as amount of hGH/rat). Then, rat blood was serially collected as time passed. The serum hGH level was measured by the radioimmunoassay (commercially available under the name of Ab beads HGH from EIKEN CHEMICAL CO., LTD.) to evaluate the hGH release profile. The immuno-suppressed SD rat was prepared by subcutaneous injection of Prograf™ (commercially available from Fujisawa Pharmaceutical Co., Ltd.) in the amounts of 0.4 mg/rat 3 days before the first administration of the microcapsules, of 0.2 mg/rat at the time of the first administration, and of 0.2 mg/rat on 4th day, 7th

day, 11th day and 14th day after the first administration. The results are shown in Fig. 1.

As obviously understood from the results of Fig. 1, the blood hGH level after administration of the microcapsules prepared by using the hGH powder obtained by application is higher than that after administration of the microcapsules prepared by using the powder obtained by spraying. These results show that the microcapsule preparation prepared by using the hGH powder obtained by application has higher bioavailability.

Experimental Example 2

Analysis of higher-order structure of finely divided protein powder by FT-IR

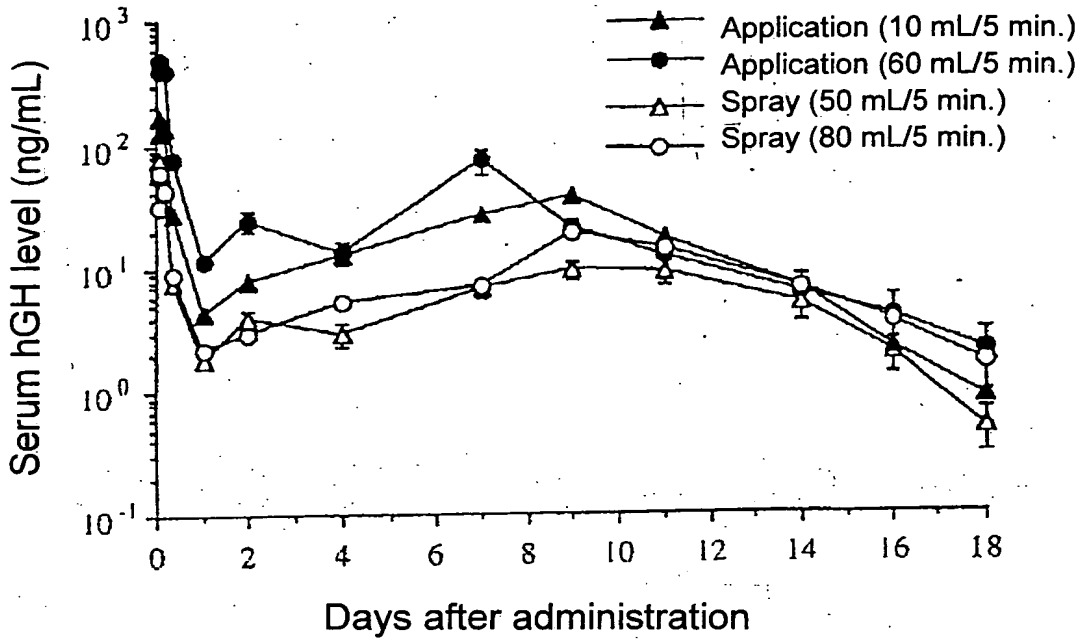
Two kinds of hGH powders, i.e., hGH powder obtained in Example 4, the amount of application of 80 (amount for 5 min. (mL)/tray) and hGH powder obtained in Example 7, the spraying amount of 80 (amount for 5 min. (mL)/tray), were subjected to analysis of higher-order structures thereof by FT-IR (Journal of Pharmaceutical Science, Vol. 87, pp. 1412-1420 (1998)). The results are shown in Table 13 as the mean ± S.D. (n=3). As seen from Table 13, the α-helix content of hGH powder obtained in Example 4 by application is much higher than that of hGH powder obtained in Example 7 by spraying. Since the α-helix content of hGH in heavy water was 59%, the hGH powder obtained in Example 7 by spraying retained 39% of α-helix in comparison with the α-helix content in heavy water. On the other

hand, the hGH powder obtained in Example 4 by application retained 59% of α-helix in comparison with the α-helix content in heavy water.

Table 13

Example 4 Application amount: amount for 5 min. 80mL /tray		Example 7 Spray amount: amount for 5 min. 80ml /tray		
wave-length (cm^{-1})	ratio	wave-length (cm^{-1})	ratio	assign-ment
1694.3 ± 0.3	3.5 ± 1.3	1694.3 ± 0.2	3.5 ± 0.4	β-sheet
1682.9 ± 0.6	18.9 ± 0.4	1684.8 ± 0.1	13.7 ± 0.2	unordered
1667.3 ± 1.8	22.3 ± 0.9	1666.9 ± 0.6	35.7 ± 1.7	unordered
1654.7 ± 0.6	31.2 ± 2.0	1653.5 ± 0.2	23.3 ± 2.0	α-helix
1641.5 ± 0.4	14.6 ± 0.7	1641.8 ± 0.3	13.8 ± 0.7	unordered
1630.1 ± 0.3	6.0 ± 0.9	1630.7 ± 0.4	6.5 ± 0.7	β-sheet
1615.8 ± 0.2	3.6 ± 0.1	1615.8 ± 0.1	3.5 ± 0.1	unordered

Fig. 1


Application (10 mL/5 min.)
Application (60 mL/5 min.)
Spray (50 mL/5 min.)
Spray (80 mL/5 min.)
Serum hGH level (ng/mL)
10^3
10^2
10^1
10^0
10^{-1}
0
2
4
6
8
10
12
14
16
18
Days after administration

7. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 30th day of September, 2003

Yutaka Yamagata

Yutaka YAMAGATA